(Liang et al., 2015), and stimulates tumor cell growth, survival, and invasiveness in response to CXCL12 secreted by the cancer cells and the surrounding cancer-associated cells (Burger and Kipps, 2006; Chatterjee et al., 2014; Domanska et al., 2013).

[0010] Systematic meta-analyses using databases including PubMed, EMBASE, and Cochrane library indicate significant association between CXCR4 over-expression and poorer progression-free survival and overall survival in various cancers including hematological malignancy, breast cancer, colorectal cancer, esophageal cancer, head and neck cancer, renal cancer, lung cancer, gynecologic cancer, liver cancer, prostate cancer, and gallbladder cancer (Du et al., 2015; Hu et al., 2015; Li et al., 2017; Wang et al., 2016; Zhao et al., 2015).

[0011] CXCR4/CXCL12 axis plays a central role in tumor growth, invasion, angiogenesis, vasculogenesis, metastasis, drug resistance, and cancer cell-tumor microenvironment interaction (D'Alterio et al., 2012; Domanska et al., 2013; Guo et al., 2016)

[0012] The critical role of CXCR4 in cancer cell proliferation and tumor growth was demonstrated in various experimental models in vitro and in vivo such as orthotopic, subcutaneous human xenograft, and transgenic mouse models using CXCR4 antagonists (Domanska et al., 2013). The Daoy medulloblastoma cells and U87 glioblastoma cells showed CXCR4 expression and exhibited dose-dependent increase in proliferation to a gradient of CXCL12 in vitro, and systemic administration of AMD3100 inhibited the growth of intracranial U87 and Daoy cell xenografts (Rubin et al., 2003).

[0013] Involvement of CXCR4 in the metastasis of cancer cells towards CXCL12 expressing organs was also demonstrated in pancreatic, thyroid, melanoma, prostate, and colon cancer xenograft models (Bartolome et al., 2009; De Falco et al., 2007; Taichman et al., 2002; Wang et al., 2008; Zeelenberg et al., 2003).

[0014] The main mechanism of action described for the small molecules or peptides antagonists of CXCR4 is centered on their ability to mobilize malignant cells from the BM, thereby sensitizing them to chemotherapy. These agents have shown limitations regarding short half-lives, making their adequate management over long periods of time difficult (Hendrix et al., 2000). In contrast, therapeutic monoclonal antibodies have the advantage of having more prolonged half-lives, and are suitable for less frequent dosing. Additionally, human IgG antibodies have the ability to induce cell death upon binding to their target protein on cancer cells, via interaction with Fc-receptor on effector cells, including antibody-dependent cell mediated cytotoxicity/phagocytosis (ADCC/ADCP) (Jiang et al., 2011). Such cytotoxic mechanism of action are not inherent to small molecules or peptides, and have been demonstrated to play a key role in the clinical activity of several therapeutic antibodies (Wang et al., 2015).

[0015] Targeting CXCR4 using a neutralizing anti-CXCR4 antibody or CXCR4 specific antagonists inhibited primary tumor growth as well as metastasis to secondary organs in breast cancer, colon cancer, hepatocellular carcinoma, osteosarcoma, and melanoma (De Falco et al., 2007; Hassan et al., 2011; Huang et al., 2009; Kim et al., 2008; Muller et al., 2001; Schimanski et al., 2006; Smith et al., 2004; Zeelenberg et al., 2003). In a transgenic breast cancer mouse model, inhibition of CXCR4 with CTCE-9908 reduced not only the growth of primary tumor but also the expression of vascular endothelial growth factor (VEGF) and AKT phosphorylation (Hassan et al., 2011).

[0016] Cancer stem cells (CSCs) are a population of cancer cells with properties such as infinite self-renewal, potential to differentiate into multiple cancer lineages, ability to adopt a quiescent state, and intrinsic high resistance to chemo- and radio-therapy. CSCs are considered as the major cause of cancer relapse and recurrence after standard anti-proliferative therapy. Therefore, targeting cancer stem cells are expected to provide more effective therapeutic interventions to eradicate the cancer and prevent relapse (Batlle and Clevers, 2017; Reya et al., 2001; Wurth, 2016). Interestingly, CSCs also express CXCR4, and CXCR4 directs the trafficking and metastasis of these cells to the CXCL12-rich microenvironments such as bone marrow and subventricular zone in the brain that favor cancer stem cell maintenance, survival and growth. CXCR4 antagonists have been shown to mobilize CSCs from these protective microenvironments, and sensitize them to conventional chemo- and radiotherapy, and anti-angiogenic therapy (Burger and Kipps, 2006; Burger and Peled, 2009; Furusato et al., 2010; Redondo-Munoz et al., 2006; Walenkamp et al., 2017; Wurth, 2016).

[0017] Increasing evidence showed that tumor mass contains various cell types such as stromal fibroblasts, immune cells, endothelial cells, connective tissue, and extracellular matrix in addition to cancer cells that constitute tumor microenvironment (TME) or cancer cell niches. CXCR4/CXCL12 axis plays pivotal roles in tumor cell-microenvironment interaction that support tumor structure, growth, angiogenesis, and evasion of immune surveillance in various cancers of both the hematopoietic and nonhematopoietic system (Burger and Kipps, 2006; Burger and Peled, 2009; Walenkamp et al., 2017). CXCL12 can promote tumor angiogenesis by recruiting endothelial cells to the TME directly, or indirectly by attracting CXCR4-positive inflammatory cells to the tumor mass, and making them to secret proangiogenic factors (Owen and Mohamadzadeh, 2013; Walenkamp et al., 2017).

[0018] Growing evidence indicates that CXCR4/CXCL12 axis contributes to the lack of tumor responsiveness to angiogenesis inhibitors. Vascular endothelial growth factor (VEGF) was considered as the major pro-angiogenic factor in cancer, and was targeted for anti-angiogenic therapy in patients with rectal carcinoma using an anti-VEGF antibody bevacizumab (Genentech). Surprisingly, bevacizumab increased the expression of CXCL12 and CXCR4 in cancer cells, and increased plasma levels of CXCL12 in these patients were associated with rapid disease progression and metastasis (Owen and Mohamadzadeh, 2013; Xu et al., 2009). Therefore, the efficacy of a combination therapy using bevacizumab and plerixafor was evaluated for recurrent glioma (ClinicalTrials.gov identifier: NCT01339039). However, the study was terminated due to a low accrual rate (Walenkamp et al., 2017).

[0019] Inhibition of CXCR4/CXCL12 axis has been demonstrated to disrupt the tumor microenvironment (TME) and expose the tumor cells to immune attack by decreasing the infiltration of myeloid-derived suppressor cells, by increasing the ratio of CD8+ cytotoxic T cells to Treg cells, or eliminating tumor re-vascularization (Burger et al., 2011; Domanska et al., 2013; Walenkamp et al., 2017). Administration of CXCR4 antagonists, AMD3100 or T22, acted synergistically with immune checkpoint inhibitors such as